Alpha Adrenoceptor Antagonists
Beta Adrenoceptor Antagonists
Ganglion-Blocking Drugs

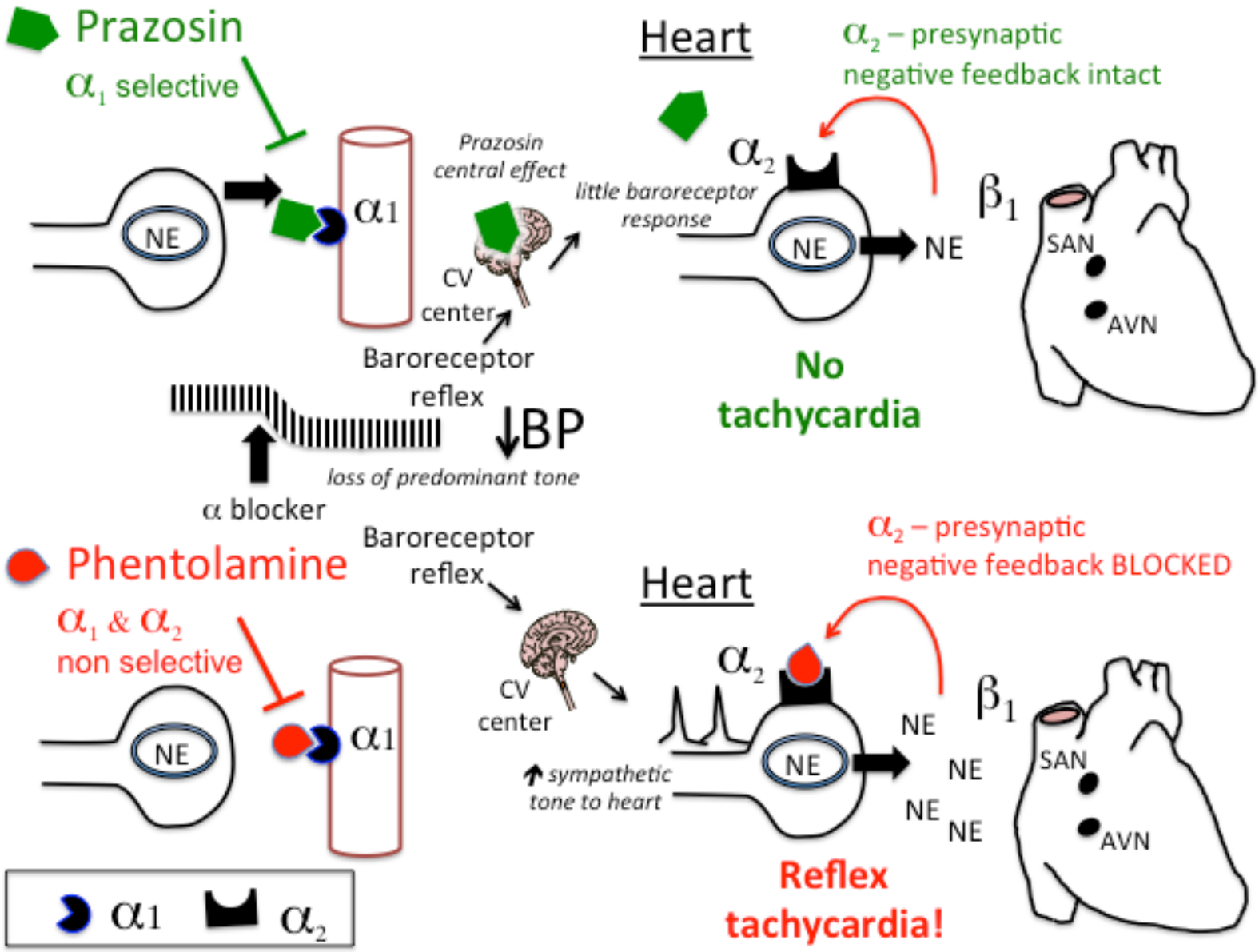
Alpha-Receptor Antagonist Drugs

Pharmacologic Effects

Cardiovascular Effects

- ↓ peripheral vascular resistance and blood pressure.
- Prevent the pressor effects of α agonists
- often cause orthostatic hypotension and reflex tachycardia; nonselective (α 1 = α 2,) blockers cause tachycardia if blood pressure is lowered below normal.

Effects of selective & Non selective alpha blockers on HR



Other Effects

- **miosis** and nasal stuffiness.

- **Alpha1** receptors are expressed in the base of the bladder and the prostate, and their blockade decreducereases resistance to the flow of urine and reduce urinary urgency.
- Alpha blockers are used for the treatment of urinary retention due to prostatic hyperplasia .

Non selective alpha blockers

Phenoxybenzamine

Binds covalently to α receptors, causing irreversible blockade of long duration (14–48 h).

Blocks α1& to less extent α2 receptors.

Also inhibits reuptake of NE and blocks histamine (H1), ACh, and serotonin receptors.

Causes little fall in BP in normal supine individuals, it reduces BP when sympathetic tone is high, e.g., as a result of upright posture.

Absorbed poorly but usually given orally.

Uses: treatment of **pheochromocytoma,** Peripheral vascular diseases

Adverse effects

Orthostatic hypotension, tachycardia, Nasal stuffiness and inhibition of ejaculation.

Phentolamine

- Rapidly acting α blocker with short duration t½ 19 min.
- Competitive α1 and α2 antagonist.
- Reduces peripheral resistance (α1) and causes cardiac stimulation (α 2 receptors blockade enhances release of NE) .
- minor inhibitory effects at 5HT receptors and agonist effects at muscarinic (salivary, sweat, lacrimal) and H1 and H2 receptors (Increase acid secretion).
- Uses: Diagnostic of pheochromocytoma, control of hypertension due to clonidine withdrawal, Cheese reaction.
- To counteract vasoconstriction due to alpha agonists..
- **Adverse effects:** severe tachycardia, arrhythmias, and myocardial ischemia.

Selective α 1 blockers
Prazosin

- Highly selective α1 blocker & less potent at α 2 receptors.
- Relaxes **both arterial and venous vascular** sm muscle

& smooth muscle in the **prostate**, due to blockade of α 1 receptors with **no or little tachycardia**

- Extensively metabolized, only 50% is available after oral administration. The half-life is **3** hours.
- Favorable effect on plasma lipids: increase HDL/LDL ratio.
- **Uses** Antihypertensive ,Benign prostatic hyperplasia (BPH) Blocks α1 in bladder trigone & prostate & decreases tone & Improves urine flow .
- **Adverse effects**: First dose phenomenon i.e. postural hypotension with initial doses.

Terazosin

High bioavailability. The half-life is 9–12 hours.

Doxazosin

Has a longer half-life of about 22 hours.

Tamsulosin

Uroselective α1A blocker. α 1A are predominant in bladder base & prostate.

30 times high affinity for α1A

High bioavailability and a half-life of 9–15 hours.

It is used to treat **BPH.**

No effect on BP and heart rate.

Side Effects: Dizziness & retrograde ejaculation.

Yohimbine

- An indole alkaloid, is **α 2-selective antagonist**. Blocks other receptors also – 5HT, DA
- Increases ADH release
- Enhances sexual activity – aphrodisiac
- Sometimes used in the treatment of **orthostatic hypotension** because it promotes NE release through blockade of presynaptic α 2 receptors.
- Was widely used to improve male **erectile dysfunction** but has been superseded by phosphodiesterase-5 inhibitors like **sildenafil (viagra).**

Uses of the Alpha-Receptor–Blocking Drugs

1- Pheochromocytoma

Causes intermittent or sustained hypertension, headaches, palpitations & increased sweating.

Phenoxybenzamine (orally) preoperative to control hypertension & for the **chronic treatment of inoperable or metastatic pheochromocytoma.**

Beta-receptor antagonists used to reverse the cardiac effects. Should not be used prior to establishing effective α -receptor blockade.

Metyrosine

α -methyltyrosine, a competitive inhibitor of **tyrosine hydroxylase.**

Used in inoperable or metastatic pheochromocytoma.

Can cause **extrapyramidal effects** due to reduced dopamine levels

2-Hypertensive Emergencies

Labetalol (α and β blocker) is used in Hypertensive Emergencies

3-Treatment of overdose of α1 agonis (phentolamine).

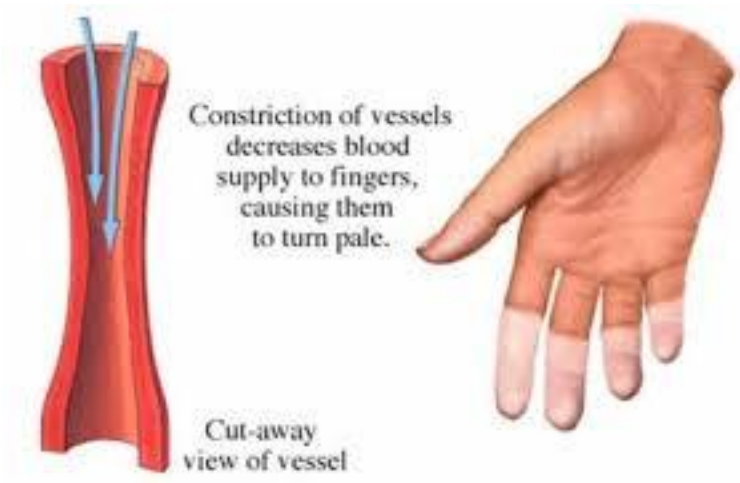
4-Chronic Hypertension

α 1-selective antagonists in mild to moderate systemic hypertension.

Not recommended as monotherapy because other drugs are more effective in preventing heart failure.

Their major adverse effect is orthostatic hypotension,

(First-Dose Phenomenon).



5-Peripheral Vascular Disease

Raynaud's phenomenon

(excessive reversible vasospasm in the peripheral circulation).

Prazosin or **phenoxybenzamine** are used but **calcium channel blockers** are preferable for most patients.

6-Urinary Obstruction

Benign prostatic hyperplasia

(BPH) is common in elderly men.

Block **α 1A-receptor** → reduced contraction of smooth muscle in the bladder neck and prostatic capsule → Reduce urinary urgency and improves urine flow.

Prazosin, doxazosin, and terazosin are all effective.

Tamsulosin is **α 1A-receptor antagonists** preferred in patients who have orthostatic hypotension with other α 1-receptor antagonists.

β- Adrenoceptor Antagonists

First generation: non selective (β1 and β 2) .

Second generation: Cardioselective (β1)

Third generation: Vasodilator β blockers.

The **selectivity is dose-related; it tends to diminish at higher drug concentrations.**

Other major differences relate to their **lipid solubility** and **local anesthetic (membrane-stabilizing)** effects. However, the concentration in plasma is **too low** for the anesthetic effects.

Most drugs are well absorbed after oral administration; peak concentrations **1–3** hours after ingestion.

- Lipophilic β blockers
  - propranolol, metoprolol, oxprenolol, carevdilol
  - readily absorbed from GI, metabolized in liver
  - large volume of distribution, and penetrate BBB well
  - hepatic failure prolongs their t1/2.

- Hydrophilic β blockers
  - acebutolol, atenolol, bisoprolol,, nadolol. sotalol
  - less readily absorbed, not extensively metabolized
  - long plasma half-lives which are prolonged in renal failure.

Pharmacodynamics

Effects on the Cardiovascular System

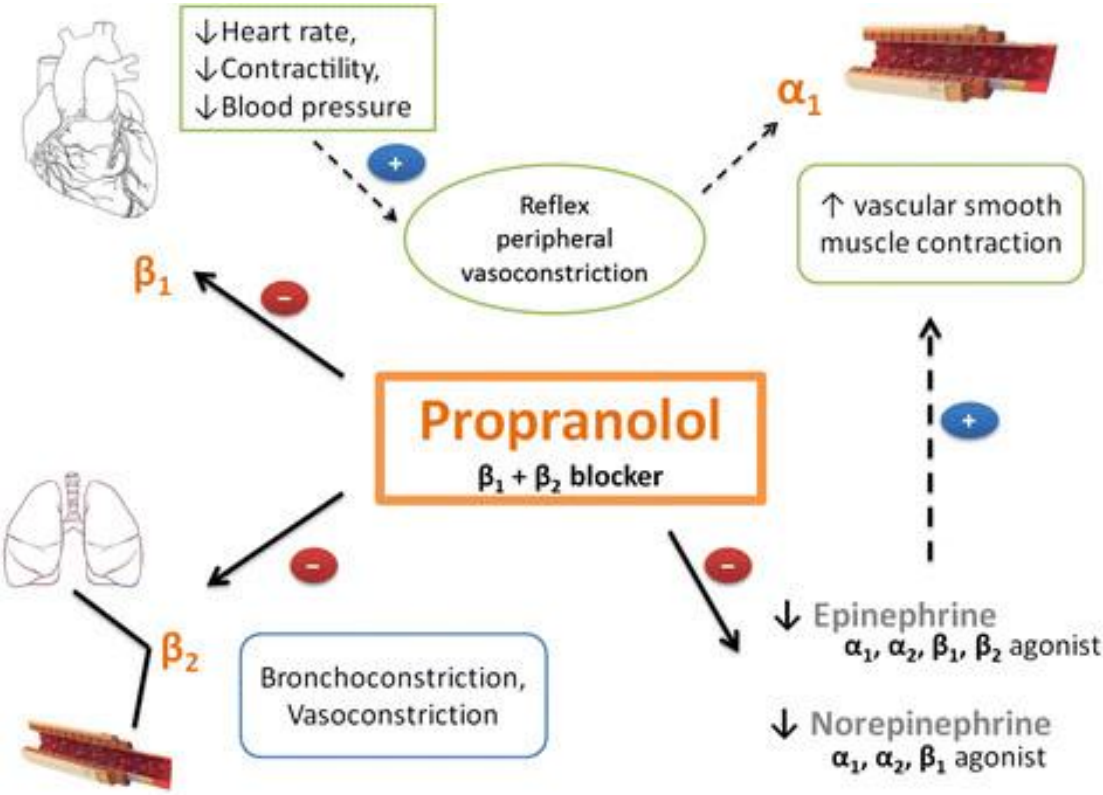
Very valuable in **hypertension, angina** and **chronic heart failure** and **following myocardial infarction (MI)**.

Heart:↓ HR, ↓SV, ↓COP. ↓ AV conduction. ↓cardiac work & O2 consumption.

Blood vessels:↓BP both diastolic and systolic after continuous treatment.

Do not cause hypotension in healthy individuals with normal BP.

Nonselective and β1-block → Inhibit renin



Effects on the Respiratory Tract

Increase in airway resistance, particularly in patients with asthma.

β1 blockers are safer than nonselective β blockers.

β 1-selective blocker are not sufficiently specific to *completely* avoid interactions with β 2 receptors.

Consequently, these drugs should generally be **avoided in patients with asthma**.

Many patients with chronic obstructive pulmonary disease may tolerate these drugs & the benefits e.g. in patients with concomitant **ischemic heart disease**, may outweigh the risks.

Effects on the Eye

Reduce intraocular pressure in **glaucoma** by decreasing aqueous humor production.

Glaucoma is treated by:

1- reduction of aqueous humor secretion.

2- enhancement of aqueous out-flow.

Drugs useful in reducing intraocular pressure:

Cholinomimetics, α agonists, β blockers

prostaglandin F2 analogs., diuretics

Prostaglandin analogs & β blockers are the most popular.

Metabolic and Endocrine Effects

- Beta-receptor antagonists increases LDL, triglycerides, ↓ HDL by inhibiting **lipolysis.**
- **Glycogenolysis** in the liver is inhibited after β 2-receptor blockade.
- β –blockers should be used with caution in **insulin-dependent diabetic patients**.

  β blockers delay recovery from hypoglycemia due to insulin and oral anti diabetics and mask early symptoms of hypoglycemia (tremors, sweating & tachycardia).

Specific Agents

Propranolol

- Prototype of β -blocking drug. High lipid solubility.
- Has low and dose-dependent bioavailability (first-pass metabolism).
- First-pass effect varies among individuals,
- A long-acting form of propranolol is available; prolonged absorption of the drug may occur over a 24-hour period.
- No effect on α and M receptors but may block some serotonin receptors in the brain, though the clinical significance is unclear.
- It has no partial agonist action at β receptors.

Other non-selective beta blockers

Nadolol

Has a **very long duration of action**.

Timolol

no local anesthetic activity used topically to treat glaucoma.

Sotalol

Nonselective that also exhibits Class III antiarrhythmic properties.

Cardioselective β Blockers (β1-selective antagonists)

less effects on bronchioles, carbohydrate metabolism, lipids.

Lower incidences of Cold hands and feet.

Less liable to impair exercise tolerance

Safer in patients who experience bronchoconstriction in response to propranolol, but their β 1 selectivity is modest, so they should be used with great caution in patients with **asthma.**

β1-selective antagonists cont..

- However, the benefits may exceed the risks, e.g., in patients with myocardial infarction.
- Beta1-selective antagonists are preferred in patients with **diabetes or peripheral vascular disease** since β 2 receptors are important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).

Metoprolol

- High lipid solubility.
- Less likely to worsen asthma.
- used to treat **angina** and **hypertension** & also used to treat or prevent Myocardial Infarction (AMI) without bradycardia.

Atenolol

- low lipid solubility. Longer duration action. One dose/day.
- Side effects related to CNS are less prominent No effect on bronchus, carbohydrate metabolism, lipids
- Most commonly used in Hypertension & angina .

Nebivolol

The **most highly selective β 1** blocker.

↑ endothelial NO release (vasodilating effect)

Antioxidant ,can protect the vascular wall from free radicals that damage blood vessels and thereby contribute to the progression of cardiovascular disease. Activates cardiac β3-adrenergic receptors (protective mechanism against heart failure and myocardial ischemia

Bisoprolol

low lipid solubility. Longer duration of action. One dose/day. used to treat hypertension, coronary heart disease, arrhythmias.

Esmolol

- Ultra-short–acting β 1-selective blocker.
- Contains an ester linkage; esterases in red blood cells rapidly metabolize it.
- Has a short half-life (about 10 minutes).
- Given by continuous IV infusions
- Esmolol may be **safer** in critically ill patients who require a β -adrenoceptor antagonist.
- Esmolol is useful in controlling **supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis and myocardial ischemia in acutely ill patients**.

β Blockers with **partial β-agonist activity.**

Effective in hypertension and angina & less likely to cause **bronchoconstriction, bradycardia and abnormalities in plasma lipids** than other β blockers.

Pindolol is a non-selective beta- adrenoceptor/5-HT1A antagonist accelerates the antidepressant effect of selective serotonin reuptake inhibitors.

Celiprolol is a β 1-selective antagonist with a **partial β2 -agonist activity** & may have less adverse bronchoconstrictor effect in asthma and may even promote bronchodilation.

Acebutolol a β 1-selective antagonist.

Drugs that block both alpha and beta receptors

Labetalol

- Causes Hypotension with less tachycardia than occurs with α blockers.
- it is a **partial agonist** at beta2- receptors

Carvedilol

- A nonselective beta blocker/alpha-1 blocker, calcium channel blocker.
- More potent at β than at α1 receptors
- Antioxidant property.
- Use: Hypertension, Angina, congestive heart failure

Clinical Uses of the Beta-Receptor–Blockers.

Hypertension

- Used alone, but often used with either a diuretic or a vasodilator.
- In spite of the short half-life of many β antagonists, these drugs **may be administered once or twice daily** and still have an adequate therapeutic effect.
- May be less effective in the **elderly** and in individuals of **African ancestry**.

Ischemic Heart Disease

Clinical Uses cont..

- Reduce the frequency of anginal episodes and improve exercise tolerance in patients with angina.
- Decrease cardiac work & reduce oxygen demand.
- Slow heart rate may contribute to clinical benefits.
- The long-term use of **timolol, propranolol,** or **metoprolol** in patients who have had a myocardial infarction prolongs survival
- β blockers are strongly indicated in the acute phase of a myocardial infarction.
- Contraindications include bradycardia, hypotension, moderate or severe left ventricular failure, shock, heart block, and active airways disease.

Cardiac Arrhythmias

Clinical Uses cont..

- Class II antiarrhythmic drugs.
- By increasing the **AV nodal refractory** period,

  β antagonists slow ventricular response rates in atrial **flutter and fibrillation**.
- They **reduce ventricular ectopic** beats, particularly if caused by catecholamines.

- **Sotalo**l has a **marked class III antiarrhythmic** effects, due to **potassium channel blockade** (treats both ventricular & supraventricular arrhythmias).

Heart Failure

Clinical Uses cont..

- Clinical trials have demonstrated that at least three β antagonists, **metoprolol, bisoprolol,** and **carvedilol** are effective in reducing mortality in selected patients with chronic heart failure.
- Although administration of these drugs may worsen acute congestive heart failure, cautious long-term use with gradual dose increments in patients who tolerate them may prolong life.
- They have a beneficial effects on **myocardial remodeling** and decrease the risk of sudden death.

- HF is characterized by β-adrenergic receptor (βAR) dysregulation that is primarily due to the upregulation of G protein–coupled receptor kinases that leads to overdesensitization of β_1 and β_2ARs, and this clinically manifests as a loss of inotropic reserve.
- The β_3AR, found in the heart, lacks G protein–coupled receptor kinases recognition sites, and is not subject to desensitization
- β_3ARs can activate different signaling pathways that can protect the heart.
- the effects of β-blockers which are well known for their cardioprotective effects, are mediated, at least in part, by enhancement of β_3AR activity.

Glaucoma

- Systemic administration of β -blocking drugs for other indications, reduced intraocular pressure in patients with glaucoma. Topical administration also reduces intraocular pressure.
- The mechanism involves reduced production of aqueous humor by the ciliary body.
- **Timolol** and related β antagonists are suitable for local use in the eye because they lack local anesthetic properties.
- Beta antagonists have an efficacy comparable to that of **epinephrine** or **pilocarpine** in open-angle glaucoma and are far better tolerated.
- Sufficient timolol may be absorbed from the eye to cause serious adverse effects on the heart and airways in susceptible individuals.

Hyperthyroidism

- Excessive CA action is important in the pathophysiology of hyperthyroidism, especially in relation to the heart
- The β antagonists are beneficial in this condition due to **blockade of adrenoceptors & in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine.**
- Propranolol has been used extensively in patients with **thyroid storm** (severe hyperthyroidism) to control supraventricular tachycardias that often precipitate heart failure.

Neurologic Diseases

- Propranolol reduces the frequency and intensity of **migraine** headache.
- Other β -receptor antagonists with preventive efficacy include **metoprolol** , **atenolol, timolol,** and **nadolol**.
- The mechanism is not known.
- β antagonists reduce certain **tremors.**
- The **somatic manifestations of anxiety** may respond dramatically to low doses of **propranolol**, particularly when taken prophylactically.
- Benefit has been found in musicians with **performance anxiety ("stage fright").**
- Propranolol may be used in symptomatic treatment of alcohol withdrawal in some patients.

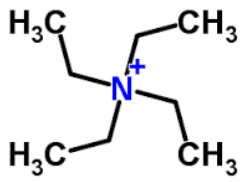
Clinical Toxicity of the Beta-Receptor Antagonist Drugs

- **Bradycardia** is the most common adverse effect. Coolness of hands and feet in winter.
- CNS effects include mild sedation, vivid dreams, and rarely, depression.
- Nonselective agents commonly causes worsening of preexisting **asthma.**
- Caution is required in patients with severe peripheral vascular disease and in patients with compensated heart failure even though long-term use may prolong life.
- A very small dose of a β antagonist may provoke severe cardiac failure in a susceptible individual.

- Beta blockers may interact with the calcium antagonist **verapamil** causing bradycardia, heart failure, and cardiac conduction abnormalities. These adverse effects may even arise in susceptible patients taking a **topical** β blocker and oral verapamil.
- Patients with ischemic heart disease or hypertension may be at increased risk if β blockade is suddenly interrupted.
- This might involve **up-regulation** of **β receptors**.
- It is inadvisable to use β antagonists in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions. **Beta1-selective antagonists** are safer in these patients

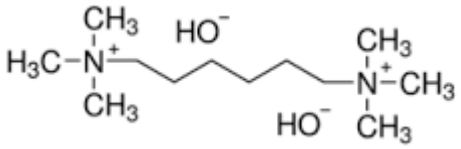
Ganglion-Blocking Drugs

Tetraethylammonium (TEA)



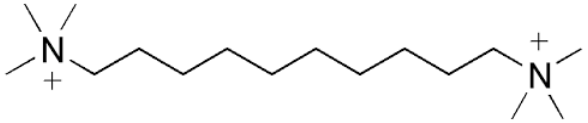
First ganglion blocker, very short duration of action.

Hexamethonium ("C6")

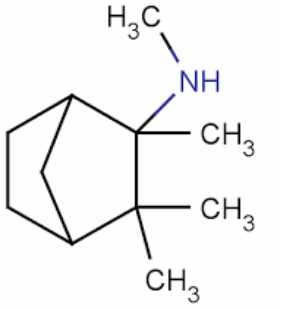


The first drug effective for hypertension.

Decamethonium, "C10" analog of hexamethonium, is a depolarizing neuromuscular blocker.

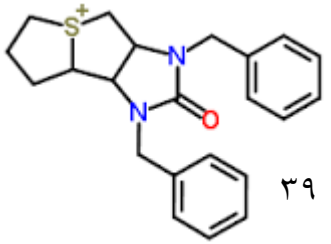


Mecamylamine



A secondary amine, developed to improve absorption from the GIT because the quaternary amine were poorly absorbed after oral administration.

Trimethaphan



A short-acting ganglion blocker, is inactive orally & is given by intravenous infusion.

Mechanism of Action

- Ganglionic nicotinic receptors are subject to both depolarizing and nondepolarizing blockade
- Nicotine & acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block.
- Drugs now used as ganglion blockers are classified as nondepolarizing competitive antagonists.
- Blockade can be reversed by increasing the concentration of an agonist, e.g., acetylcholine.

Organ System Effects

Central Nervous System

Mecamylamine enters the CNS causing Sedation, tremor, **choreiform** movements, and mental abnormalities.

Eye

- **Cycloplegia** with loss of accommodation & **moderate dilation of the pupil** because parasympathetic tone usually dominates this tissue.

Cardiovascular System

- Marked decrease in arteriolar and venomotor tone.
- **BP** may fall because both peripheral vascular resistance and venous return are decreased
- **Orthostatic or postural hypotension**, **diminished contractility** and a **moderate tachycardia**.

GIT

- Secretion & Motility are profoundly inhibited, and constipation can be marked.

Other Systems

- may precipitate urinary retention in men with prostatic hyperplasia.
- **Sexual function** is impaired in that both erection and ejaculation.
- **Sweating** is reduced by the ganglion-blocking drugs.

Clinical Applications & Toxicity

- Ganglion blockers are **used infrequently** because more selective agents are available.

Mecamylamine

- Blocks central nicotinic receptors and has been advocated as a possible adjunct with the transdermal nicotine patch to **reduce nicotine craving in patients attempting to quit smoking**.

Trimethaphan

- Occasionally used in the treatment of hypertensive emergencies and in producing hypotension in neurosurgery to reduce bleeding in the operative field.

- The toxicity of the ganglion-blocking drugs is limited to the autonomic effects.
- These effects are intolerable except for acute use.